Effectiveness of regional restrictions in reducing SARS-CoV-2 transmission during the second wave of COVID-19, Italy.

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Abstract

To counter the second COVID-19 wave, the Italian government has adopted a scheme of three sets of restrictions (coded as *yellow, orange,* and *red*) imposed on a regional basis. We estimate that milder restrictions in regions at lower risk (*yellow)* resulted in a transmissibility reduction of about 18%, leading to a reproduction number Rt of about 0.99. Stricter measures (*orange* and *red*) led to reductions of 34% and 45% and Rt values of about 0.89 and 0.77 respectively.

Starting from the end of September 2020, a second wave of COVID-19 has been spreading throughout Italy [1]. To counter the rise in SARS-CoV-2 infections, the national government has implemented a number of progressive restrictions, initially implemented homogeneously over the country, and then reflecting regional heterogeneities in the transmission and the pressure on healthcare systems [2-5].

In this work, we aim to evaluate the impact of the different restriction levels implemented on a sub-national scale in reducing SARS-CoV-2 transmission.

The study

We collected information about interventions performed in Italy since October 14 from official sources [2-10]. Between October 14 and November 5, 2020, interventions were uniformly enacted at the national level. Starting November 6, different interventions were performed at the regional scale. Three sets of measures were enacted by the central government after epidemiological risk assessments of regions based on the combination of quantitative indicators on: i) the level of transmission, ii) the burden on older age groups and healthcare, and iii) public health resilience [5]. The sets of interventions were labeled according to a color scheme: yellow, orange, and red, corresponding to increasing levels of restrictions (Table 1).

Data for the epidemic curves were collected by regional health authorities and collated by the Istituto Superiore di Sanità (Italian National Institute of Health) within an integrated surveillance system [11]. From the epidemic curves and the distribution of the serial interval [12-13], we estimated the net reproduction number Rt as a measure of transmissibility for each of the 107 Italian provinces, using a well-established method [14-17].

We applied a linear mixed model to assess the impact of regional control measures on SARS-CoV-2 transmissibility (i.e., Rt):

$$Y_{p,T} = \beta_0 + \beta_1 X_p^{orange} + \beta_2 X_p^{red} + \beta_3 Z_T + \beta_4 X_p^{orange} Z_T + \beta_5 X_p^{red} Z_T + a_r + b_{r,p} + \varepsilon_{p,T}$$

where

- $Y_{p,T}$ represents the value of Rt in each of the 107 Italian provinces (*p*), averaged over two possible time periods (*T*): October 30 to November 5 (i.e., when national-level interventions were still in place) or November 19 to November 25 (i.e., two to three weeks after the introduction of region-specific measures);
- X_p^l is a binary variable set to 1 if province *p* belongs to a region with maximum restriction level l, and 0 otherwise;
- Z_T is a binary variable set to 0 if T=October 30 – November 5 and to 1 if T=November 19 – November 25;
- $\beta_0, \beta_1, \beta_2, \beta_3, \beta_4$, and β_5 are model parameters, with β_0 representing the average value of Rt for provinces in *yellow* level during the period October 30 – November 5.
- a_r and $b_{r,p}$ are random effects, assumed to be normally distributed. a_r allows random deviations among regions from the average value of Rt. $b_{r,p}$ allows random deviations, among provinces within a region, from the regional average of Rt.
- $\varepsilon_{p,T}$ is random noise assumed to be normally distributed.

Restrictions	October 14 – November 5, 2020	November 6, 2020 – onwards		
	National-level measures	*Yellow* measures	*Orange* measures	*Red* measures
Individual movements	No restrictions	Stay-home mandate between 10pm and 5am (except for work, health and other certified reasons)	Stay-home mandate between 10pm and 5am and ban on movements between municipalities and to/from other regions (except for work, health and other certified reasons)	Stay-home mandate and ban on movements between municipalities and to/from other regions (except for work, health and other certified reasons).
Retail and Services	Open	Shopping malls closed during weekends and holidays (with the exception of essential retail & services)	Shopping malls closed during weekends and holidays (with the exception of essential retail & services)	All shops closed (with the exception of essential retail & services)
Schools & Childcare	Open until October 18. Recommendation to adopt distance learning for high schools and universities since October 19. Mandatory distance learning for at least 75% of the time in high schools since October 26. Regional exceptions: - in Campania, kindergartens were closed and distance learning for all schools adopted since October 16; - in Apulia, distance learning for all schools adopted since October 30; - in Lombardy, 100% distance learning for high schools since October 26; - in Calabria, 100% distance learning for high schools and universities since October 26.	Distance learning in high schools and universities except when on-site attendance is essential (i.e., for laboratory activities)	Distance learning in high schools and universities except when on-site attendance is essential (i.e., for laboratory activities)	Distance learning in second and third grade of middle schools, in all grades of high schools and universities
Bars serving food, Cafès & Restaurants	No service after 12am until October 25. No service after 6pm and take away allowed until 12am since October 26.	No service after 6pm and take away allowed until 10pm.	Closed. Take away allowed until 10pm.	Closed. Take away allowed until 10pm.
Public transport	No capacity reduction In Umbria, 50% capacity reduction since October 21.	50% capacity reduction (except school service)	50% capacity reduction (except school service)	50% capacity reduction (except school service)
Indoor recreational and cultural venues	Open with capacity reduction until October 25. Closed since October 26.	Closed	Closed	Closed
Gyms, pools & leisure venues	Open until October 25. Non-professional contact sports not permitted. Closed except outdoor sport centers since October 26.	Closed except outdoor sport centers	Closed except outdoor sport centers	Individual outdoor training only (except sport events of national interest)

Table 1. Description of restrictions applied in Italy between October 14 and still valid at the time of writing. Data from [2-10].

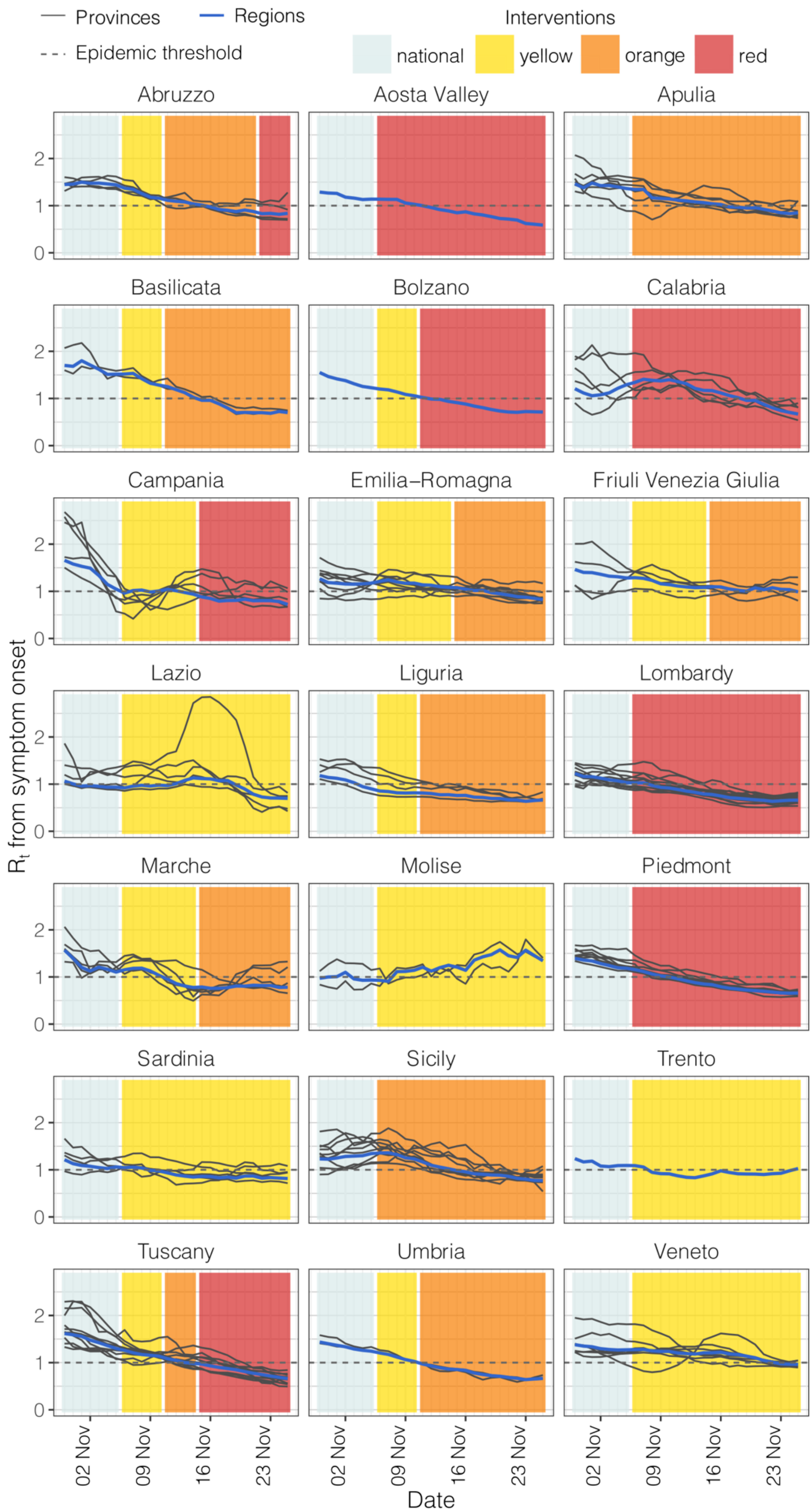

Figure 1 Temporal dynamics of the net reproduction numbers Rt and of the restriction levels applied between October 30 and November 25. Each line shows the mean Rt for an Italian province (black) or region (blue). Provinces are grouped by region as interventions were carried out at the regional level. Colored rectangles refer to the timeframe when the different sets of interventions were adopted (see Tab. 1 for color codes).

Impact of restrictions levels on transmissibility

The temporal dynamics of Rt, as well as the timing of implementation of the three levels of interventions, were highly variable by region and province (Fig. 1). Eleven of 21 regions/autonomous provinces maintained the same level of restrictions throughout the study period; for all remaining regions except Abruzzo, the highest level of restriction corresponded also to the one which has been maintained for the longest time.

The model estimated an average absolute reduction in Rt of 0.22 (95%CI: 0.10 - 0.35) for the least restrictive interventions (*yellow*). On top of this reduction, we estimated an additional reduction of 0.24 (95%CI: 0.09 - 0.39) for the intermediate level of interventions (*orange*), and an additional 0.40 (95%CI: 0.26 - 0.55) reduction for the most restrictive measures (*red*) (Appendix). The net reproduction number fell below the epidemic threshold in 42 of 46 (91%) provinces in red regions, in 33 of 41 (81%) provinces in orange regions and only in 10 of 20 provinces in yellow regions (50%), despite the latter starting from a much lower Rt value (Fig. 2, Appendix).

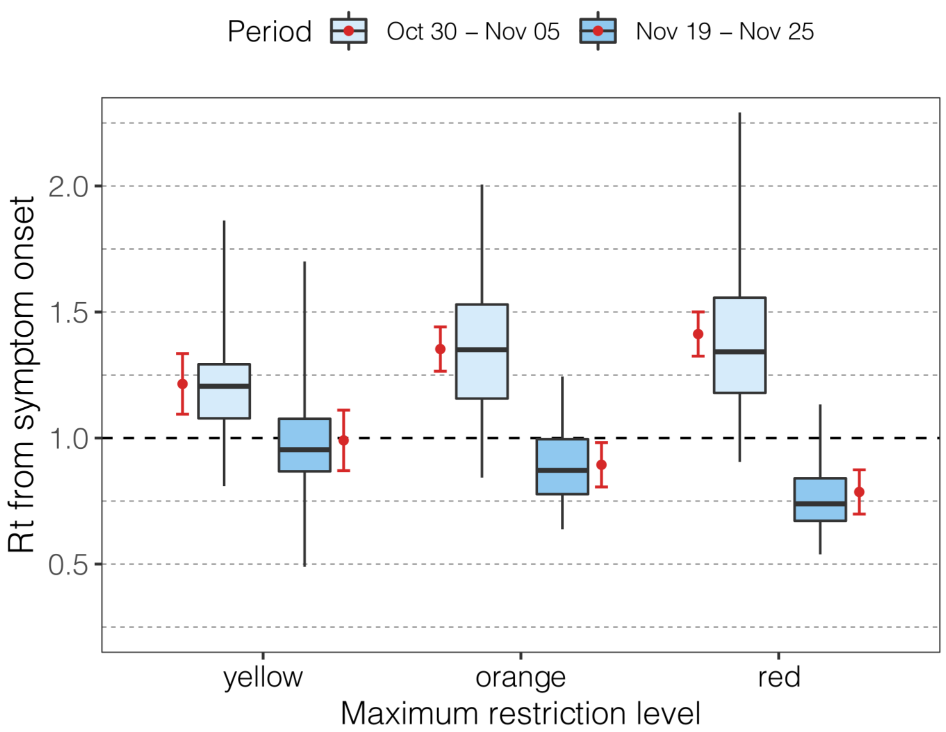

Figure 2 Distribution of the estimated reproduction numbers Rt across provinces aggregated according to the maximum level of regional restrictions and period of observation, with the corresponding fit from the linear mixed model. Boxplots represent the median, interquartile range and 95% quantiles of the Rt distributions. Red dots represent the mean of the model fit and red vertical lines represent the 95% confidence interval around the mean.

Discussion

Our results suggest that the additional restrictions implemented on a regional basis by the Italian government since November 6, 2020 were effective in reducing the transmissibility of the second wave of COVID-19. Milder restrictions (*yellow*) implemented in regions considered at lower risk provided a transmissibility reduction which brought Rt to values close to 1, resulting in an approximately constant incidence. Stricter restrictions (*orange* and *red*) were both able to bring the reproduction number significantly below the epidemic threshold, even though starting from higher values, resulting in a decreasing incidence. Overall, provinces enacting *yellow* measures achieved a 18.4% reduction of Rt with respect to the transmission level determined by the preceding nationwide interventions while a reduction of 34.0% and 44.9% was observed for *orange* and *red* measures respectively (Appendix).

Results were robust when aggregating the analysis at the regional level (although with lower statistical power due to the lower number of data points), when the reproduction number was estimated from the curve of hospitalized cases, and when considering alternative lengths of the observation periods (from 3 to 12 days) (Appendix).

We acknowledge that during high incidence periods there may be significant changes in notification rates due to the saturation of tracing and testing capabilities [15-16]; this may lead to biases in the estimates of the reproduction numbers. During the second wave, the largest increase in the number of cases occurred in October; therefore, we expect the notification rate to have stabilized before the study period (October 30 – November 25). Notification rates are less subject to changes for hospital admissions, and we found similar results when using these data to estimate transmissibility.

National interventions implemented by the Italian government were scaled up in three different occasions (on October 13, 18 and 24 [2-4]) before adopting the color-based regional classification system since November 6, 2020. It is therefore possible that part of the decrease of Rt after November 6 is associated to a residual effect of earlier interventions. Previous studies [17] have shown that most of the reduction in Rt takes place within about two weeks after the introduction of restrictions. Therefore, this limitation should not have a major effect on our conclusions, and especially on the additional effect of *orange* and *red* restrictions levels compared to the *yellow* one. Relatedly, our assumption to classify regions based on their maximal restrictions may not appropriately reflect the dynamical changes in restriction levels occurring for about half of Italian regions (Fig. 1). To evaluate possible biases arising from this assumption, we run a sensitivity analysis where we categorize regions in five groups: regions with *yellow*, *orange,* and *red* levels of restrictions throughout the study period, and regions which had different restrictions levels reaching up to either the *orange* or the *red* level. The obtained results were substantially equivalent to those presented in the main text, although with lower statistical power (Appendix).

Finally, we stress that our analysis is not suitable to pinpoint which specific interventions maximized the Rt reduction [18, 19], to disentangle the effect of spontaneous behavioral changes, and could not capture possible cross-regional effects. For example, provinces performing *yellow* level measures and sharing borders with regions performing *orange* or *red* measures may have indirectly benefited from a reduction of inter-regional mobility or that residents were more prone to self-imposing restrictions to their activity patterns.

Conclusion
This study provides a timely assessment of the effectiveness of heterogeneous interventions adopted in Italy on a regional basis, which is essential to support the ongoing effort to curtail the second wave of COVID-19 and to plan the response to possible future resurgence of cases.

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Appendix

1. Additional results of the main analysis

Figure S1. Timeframe of interventions in each Region and the Autonomous Provinces (AP) of Trento and Bolzano.

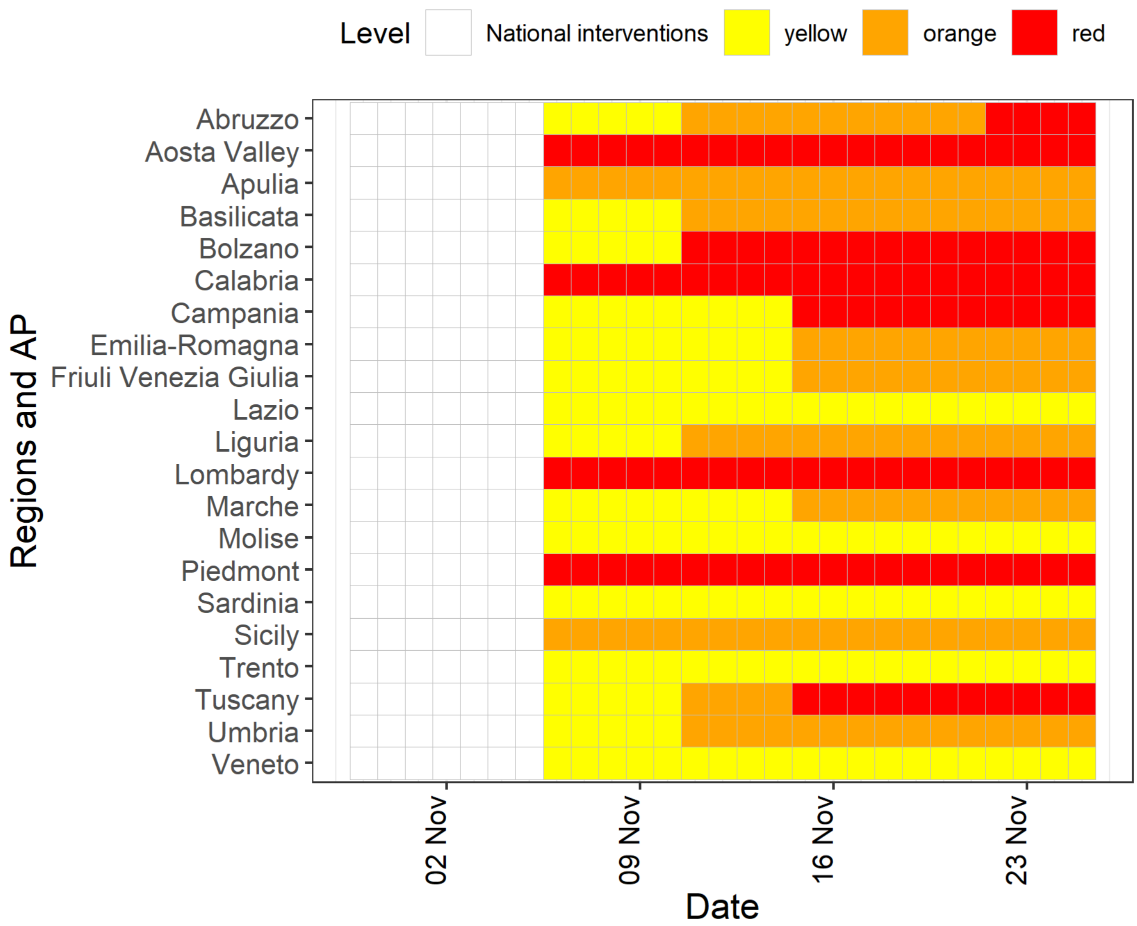


Figure S2 Variation of the net reproduction number Rt in each province. The arrows indicate the variation in Rt from the week before the introduction of the regional system of colour-coded measures (October 30-November 5) to the end of our observations (November 19 – 25). Provinces are ordered by decreasing reduction in Rt.

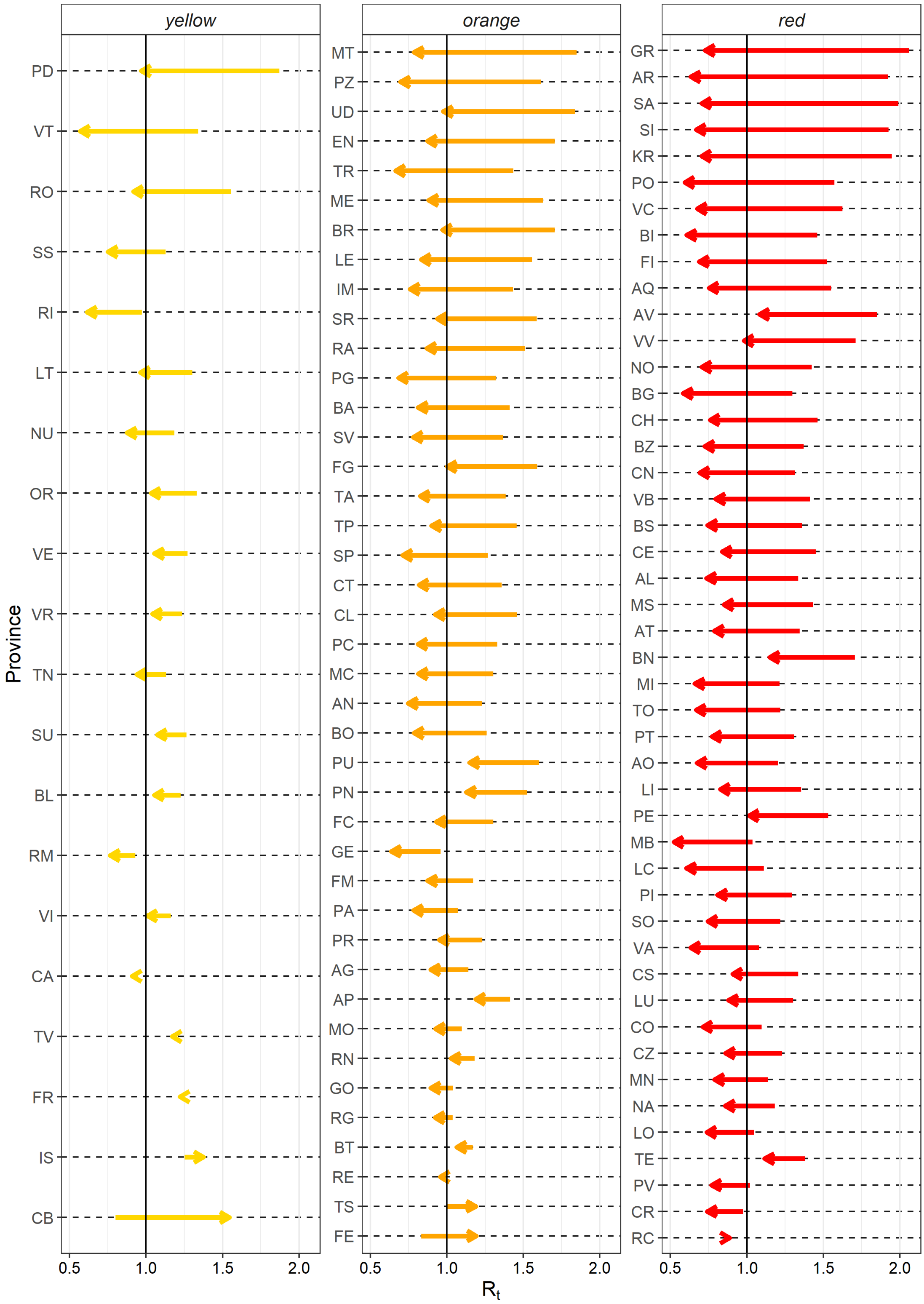


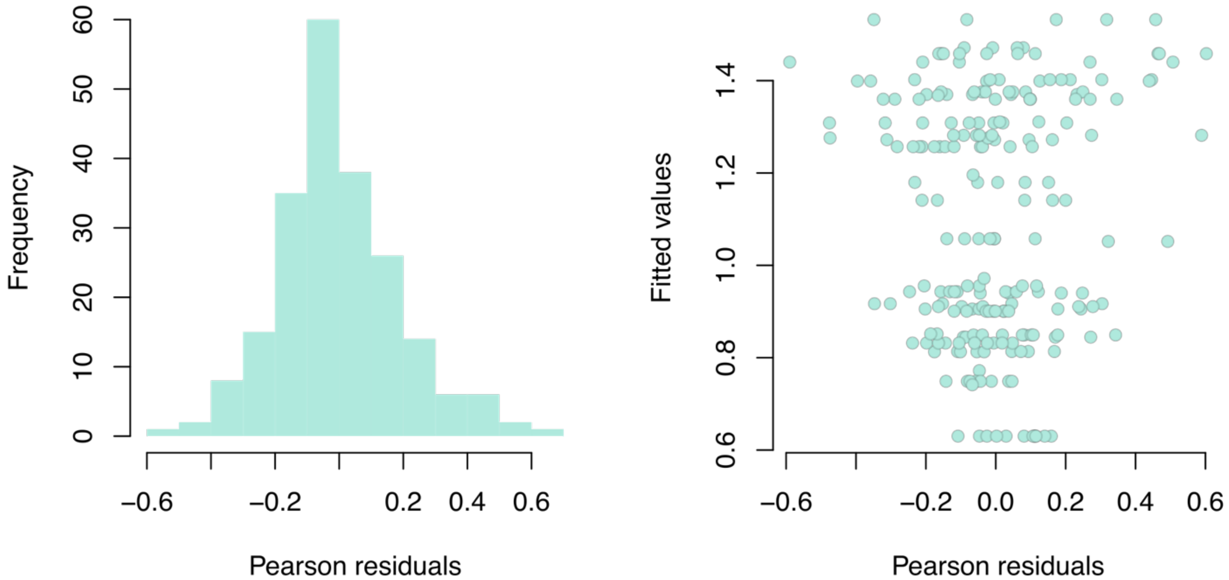
Table S1. Results of the linear mixed model on the net reproduction number Rt at provincial level. The estimated standard deviation for the random effect between regions, a_r, was 0.09, while the one for the random effect between provinces of the same region, $b_{p,r}$ was $7{\cdot}10^{-10}$. The estimated standard deviation for random noise, $\varepsilon_{p,T}$, was 0.20.

Parameter	Interpretation	Value	Std Error	DF	t-value	p-value
β_0	Mean Rt before interventions for provinces in regions with maximum restriction level *yellow*	1.215	0.061	37.8	18.830	<0.00001
β_1	Difference in the mean Rt before interventions for provinces in regions with maximum restriction level *orange,* compared to *yellow*	0.138	0.076	35.3	1.821	0.07708
β_2	Difference in the mean Rt before interventions for provinces in regions with maximum restriction level *red,* compared to *yellow*	0.198	0.076	33.6	2.608	0.01348
β_3	Reduction in Rt after interventions for provinces in regions with maximum restriction level *yellow*	-0.224	0.063	193.2	-3.559	0.00047
β_4	Additional reduction in Rt after interventions for provinces in regions with maximum restriction level *orange*, on top of reduction afforded by *yellow*	-0.235	0.077	193.2	-3.063	0.00251
β_5	Additional reduction in Rt after interventions for provinces in regions with maximum restriction level *red*, on top of reduction afforded by *yellow*	-0.402	0.076	193.2	-5.341	<0.00001

Table S2 Estimates of the net reproduction number Rt across regions with different restriction levels, before and after regional interventions.

Maximum restriction level	**Mean Rt (standard deviation) October 30 – November 5**	**Mean Rt (standard deviation) November 19 - 25**	**Relative reduction**
yellow	1.21 (0.23)	0.99 (0.23)	18.4%
orange	1.35 (0.24)	0.89 (0.14)	34.0%
red	1.40 (0.29)	0.77 (0.14)	44.9%

Figure S3. Analysis of residuals for the linear model. Left: distribution of Pearson residuals (i.e., raw residuals normalized with respect to the variance of residuals); right: scatterplot between Pearson residuals and fitted values of $Y_{p,T}$.



2. Sensitivity analysis

We evaluated the robustness of our results by re-running the main sensitivity analyses with alternative modelling choices. In particular, we considered the following five sensitivity analyses:

1) **Hospital admission.** We used the same model as described in the main text, but considering as dependent variable $Y_{p,T}$ the reproduction number from hospital admissions, Rt^h, by province and period of observation;

2) **Regional analysis.** we used the following model

$$Y_{r,T} = \beta_0 + \beta_1 X_r^{orange} + \beta_2 X_r^{red} + \beta_3 Z_T + \beta_4 X_r^{orange} Z_T + \beta_5 X_r^{red} Z_T + a_r + \varepsilon_{r,T}$$

which is analogous to the one described in the main text, but considering as dependent variable $Y_{r,T}$ the regional values of Rt, and where the independent variables are region-specific;

3) **Regional analysis on hospital admission.** We used the same model as in (2) but using as dependent variable $Y_{r,T}$ the regional values of Rt^h;

4) **Alternative time frame.** We considered a number of different lengths of periods T for the evaluation of $Y_{p,T}$;

5) **Alternative categorization of restrictions.** We considered a finer categorization of regions with 5 restriction levels rather than 3, to account for the temporal evolution of regional restrictions.

2.1 Hospital admission

Figure S4 shows the estimated Reproduction number from hospital admissions (Rt^h) curves for the 107 Italian provinces and regions, as well as restriction levels attributed to each region over time. The obtained results are reported in Tab. S3, Fig. S5, and Tab. S4.

Figure S4 Temporal dynamics of the net reproduction numbers from hospital admissions, Rt^h, and of the restriction levels applied between October 30 and November 25. Each line shows the mean Rt^h for an Italian province or region. Provinces are grouped by region as interventions were carried out at the regional level. Coloured rectangles refer to the timeframe when the different packages of interventions were adopted (see Tab. 1 in main text for a description of restrictions corresponding to each colour).

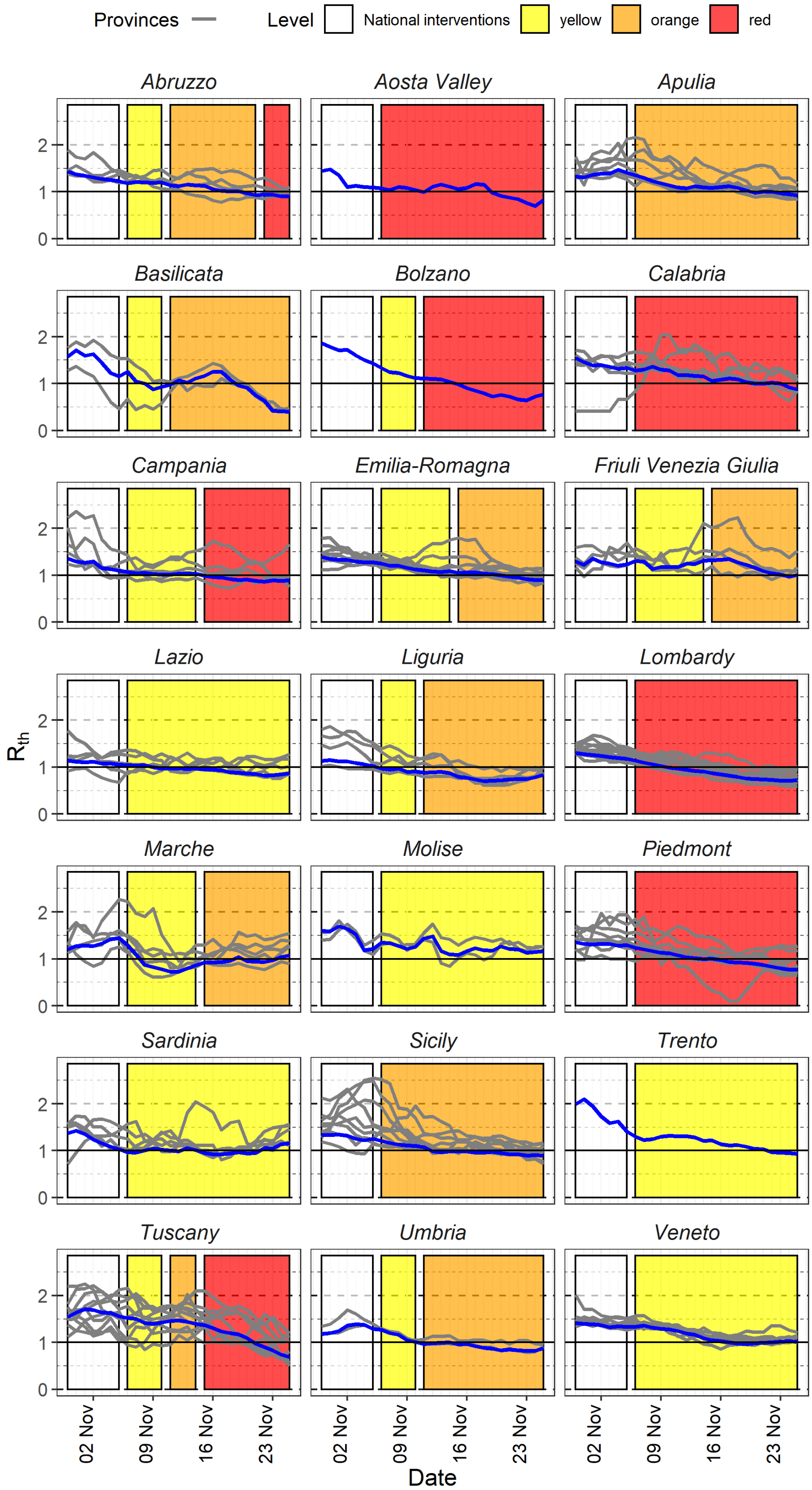


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Table S3. Result of the linear mixed model on the net reproduction number estimated from hospital admissions, Rt^h, at the provincial level.

Parameter	Value	Std Error	DF	t-value	p-value
β_0	1.393	0.062	39.8	22.478	<0.00001
β_1	0.067	0.077	37.0	0.873	0.3883
β_2	0.045	0.077	34.9	0.593	0.5568
β_3	-0.280	0.067	193.1	-4.191	<0.00001
β_4	-0.162	0.082	193.1	-1.991	0.0479
β_5	-0.192	0.080	193.1	-2.399	0.0174

Figure S5 Variation in the net reproduction number from hospital admissions (Rt^h) in each province. The arrows indicate the variation in Rt^h from the period before the introduction of the regional system of colour-coded measures (October 30-November 5) to the end of our observations (November 19 – 25). Provinces are ordered by decreasing reduction in Rt^h.

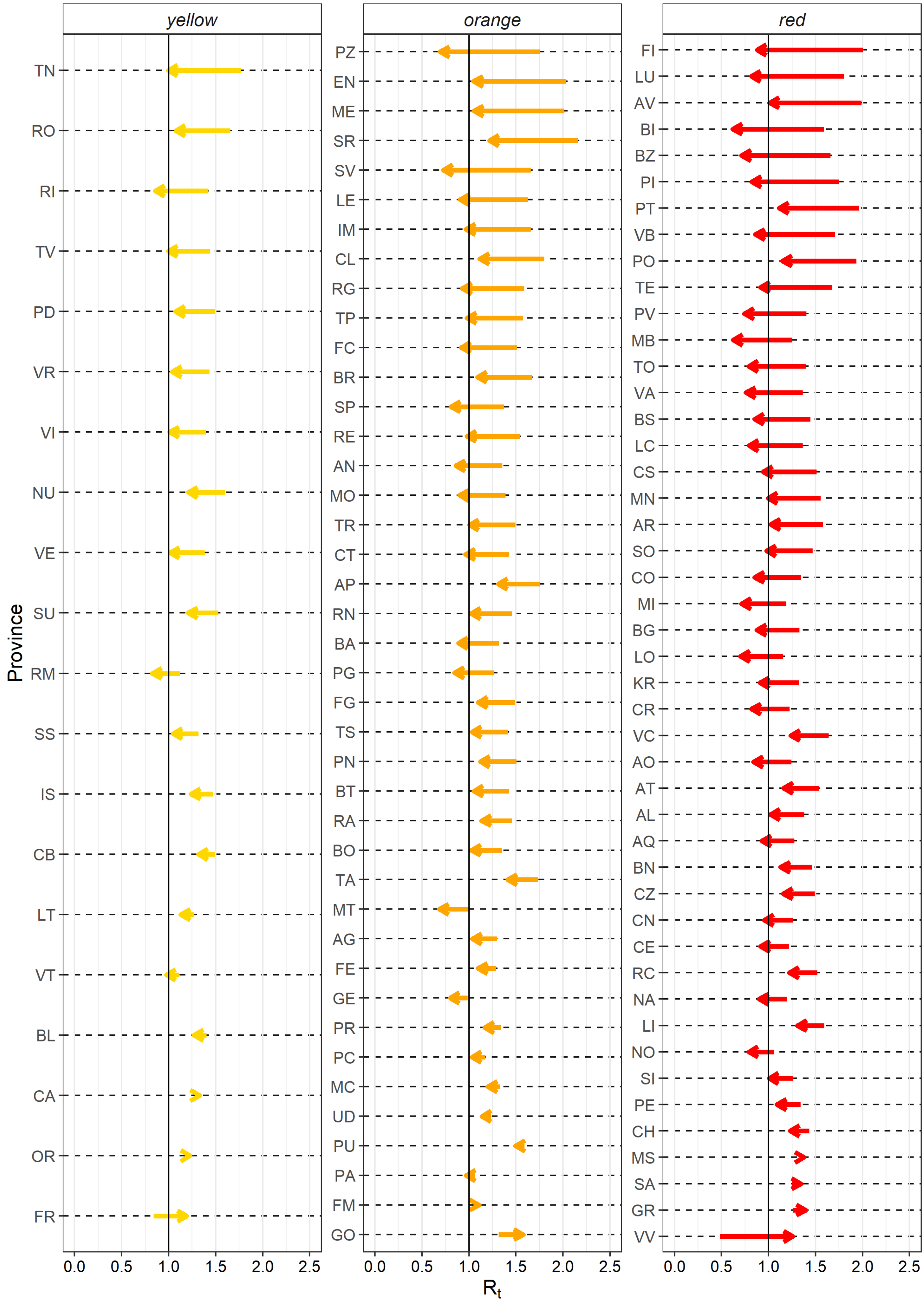


Table S4 Estimates of the net reproduction number from hospital admissions Rt^h , across regions with different restriction levels, before and after regional interventions.

Maximum restriction level	**Mean Rt^h (standard deviation) October 30 – November 5**	**Mean Rt^h (standard deviation) November 19 - 25**	**Relative reduction**
yellow	1.38 (0.21)	1.10 (0.14)	20.3%
orange	1.48 (0.26)	1.03 (0.19)	30.4%
red	1.44 (0.27)	0.97 (0.20)	32.6%

2.2 Regional analysis

We applied the same linear mixed model to the Rt values computed at regional rather than at provincial level. Table S5 reports model results for Rt computed from symptom onset, which are compliant with results obtained at provincial level, although they show lower statistical power due to the lower number of observations.

Table S5. Result of the linear mixed model on the net reproduction number estimated from symptom onset, Rt, at the regional level.

Parameters	**Value**	**Std Error**	**DF**	**t-value**	**p-value**
β_0	1.099	0.069	35.9	15.810	<0.00001
β_1	0.217	0.089	35.9	2.453	0.01914
β_2	0.211	0.089	35.9	2.382	0.02265
β_3	-0.087	0.096	18	-0.909	0.37562
β_4	-0.415	0.123	18	-3.389	0.00327
β_5	-0.478	0.123	18	-3.901	0.00105

2.3 Regional analysis on hospital admission

Tab. S6 reports similar findings to Tab. S5 starting from the reproduction number estimated from the time series of hospital admissions.

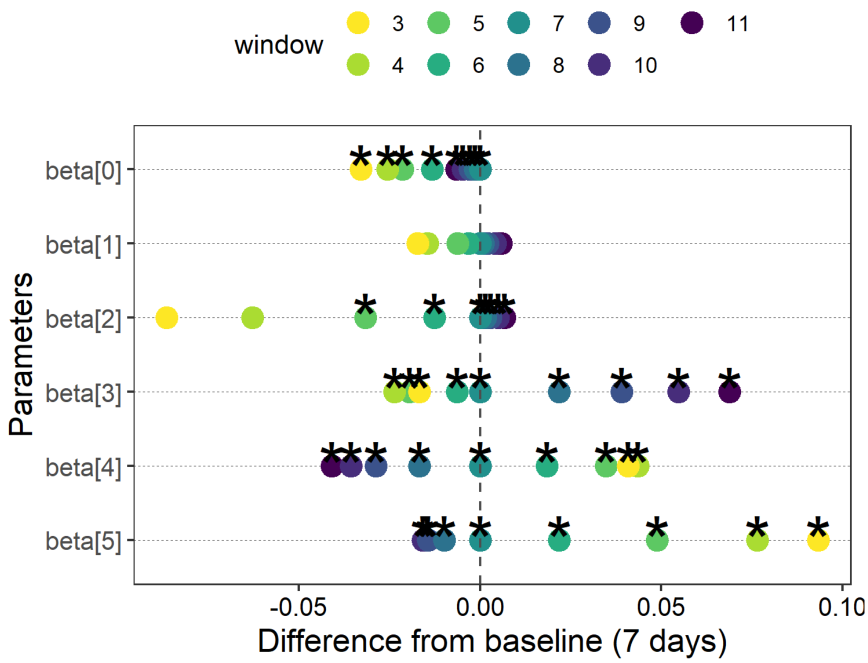
Table S6. Result of the linear mixed model on the net reproduction number estimated from hospital admission date, Rth, at the regional level.

Parameters	Value	Std Error	DF	t-value	p-value
β_0	1.393	0.067	35.8	20.690	<0.00001
β_1	-0.088	0.086	35.8	-1.025	0.31246
β_2	-0.015	0.086	35.8	-0.171	0.86501
β_3	-0.378	0.092	18	-4.109	0.00066
β_4	-0.032	0.117	18	-0.271	0.78921
β_5	-0.144	0.117	18	-1.233	0.23357

2.4 Alternative time frame

We applied the same linear mixed model to the Rt values computed at provincial level but within different period lengths ranging from 3 to 11 days. For example, when considering a period length of 3 days, we compared the mean Rt in period November 3 – 5 (before regional interventions) against November 23-25. Figure S6 shows the difference between the model parameters estimated for each period length compared to the baseline (7 days). Estimated variations in parameter estimates are small, confirming the robustness of results in the main analysis.

Figure S6 Variation in estimated model parameters when considering different lengths (in days) of the window over which Rt is averaged. On the x axis the difference between the estimated parameter value of the parameter and the corresponding baseline (using a 7-day window). Parameter names are on the y axis. Colours represent different period lengths. Asterisks represent statistical significance of the estimated model parameters (p-value <0.05).



2.5 Alternative categorization of restrictions

In this sensitivity analysis, we categorize regions in five groups (see Figure S1 for reference):

- L1: restriction level constantly yellow (20 provinces): Lazio (5 provinces), Molise (2 provinces), Sardinia (5 provinces), Trento (1 Autonomous Province), Veneto (7 provinces);
- L2: restriction level reaching up to orange (26 provinces): Basilicata (2 provinces), Emilia-Romagna (9 provinces), Friuli Venezia Giulia (4 provinces), Liguria (4 provinces), Marche (5 provinces), Umbria (2 provinces);
- L3: restriction level constantly orange (15 provinces): Apulia (6 provinces), Sicily (9 provinces)
- L4: restriction level reaching up to red (20 provinces): Abruzzo (4 provinces), Bolzano (1 autonomous province), Campania (5 provinces), Tuscany (10 provinces);
- L5: restriction level constantly red (26 provinces): Aosta Valley (1 province), Calabria (5 provinces), Lombardy (12 provinces), Piedmont (8 provinces).

The obtained results were substantially equivalent to those presented in the main text (see Table S7).

Table S7 Result of the linear mixed model on the net reproduction number estimated from symptom onset Rt at provincial level considering 5 groups of interventions

Parameter	Interpretation	Value	Std Error	DF	t-value	p-value
β_0	Mean Rt before interventions for provinces in regions with restriction level L1	1.215	0.055	35.1	22.001	<0.00001
β_1	Difference in the mean Rt before interventions for provinces in regions L2, compared to L1	0.103	0.074	34.8	1.404	0.16908
β_2	Difference in the mean Rt before interventions for provinces in regions L3, compared to L1	0.207	0.089	23.7	2.319	0.02933
β_3	Difference in the mean Rt before interventions for provinces in regions L4, compared to L1	0.345	0.080	30.6	4.304	0.00016
β_4	Difference in the mean Rt before interventions for provinces in regions L5, compared to L1	0.071	0.077	26.5	0.921	0.36516
β_5	Reduction in Rt after interventions for provinces in regions L1	-0.224	0.062	190.5	-3.598	0.00041
β_6	Additional reduction in Rt after interventions for provinces in regions L2, on top of reduction afforded by L1	-0.199	0.083	190.5	-2.401	0.01733
β_7	Additional reduction in Rt after interventions for provinces in regions L3, on top of reduction afforded by L1	-0.299	0.095	190.5	-3.133	0.00200
β_8	Additional reduction in Rt after interventions for provinces in regions L4, on top of reduction afforded by L1	-0.512	0.088	190.5	-5.820	<0.00001
β_9	Additional reduction in Rt after interventions for provinces in regions L5, on top of reduction afforded by L1	-0.32	0.083	190.5	-3.842	0.00017